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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SCHNIZER, RICHARD A	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 07/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/555,574	BEHR ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *17 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1,2,5-33,37-41,45,46,48 and 49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1,2,5-33,37-41,45,46,48 and 49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 October 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/14/2000*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The Examiner in charge of this Application has changed. Please direct further correspondence to Richard Schnizer, Art Unit 1635. Contact information is given at the conclusion of the Action.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/17/04 has been entered.

Claims 1, 2, 5-33, 37-41, 45, 46, 48, and 49 remain pending and are under consideration in this Office Action.

Information Disclosure Statement

The form 1449 filed 9/14/00 has been initialed and signed by the Examiner.

Rejections Withdrawn

The rejection of claims 1, 2, 5-33, 37-41, 45, 46, 48, and 49 under 35 USC 112, first paragraph for lacking enablement is withdrawn. The rejection was largely based on the unpredictability of forming liposomes. However, but the

claims do not require formation of liposomes, and the prior art is replete with transfection particles formed from non-vesicular polyplexes comprising cationic molecules with lipophilic residues and non-toxic backbones.

Drawings

The formal drawings filed 10/23/00 have been approved by the Draftsman.

Specification

The Examiner made minor amendments to the Brief Description of the Drawings to indicate that Fig. 4 contains panels A-D and Fig. 16 contains panels A-C.

Claim Objections

Claim 8 is objected to because it is ungrammatical. The word "is" should be deleted at page 5, lines 6 and 9 of the submission of 8/21/03. Similar alterations should be made to the corresponding sections of claim 49.

Claims 16 and 18 are objected to because "claim" should be plural.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 5-33, 37-41, 45, 46, and 49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 2, 5-33, 37-41, 45, 46, and 49 are indefinite because they recite "the precursor molecules" without proper antecedent basis. Claims 1 and 49 recite two antecedents: "identical" and "different" organic cationic precursor molecules. It is unclear to which of these "the precursor molecules" refers.

Claims 1, 2, 5-33, 37-41, 45, and 46 are indefinite because they recite "said precursor molecules" without proper antecedent basis. Claim 1 recites two antecedents: "identical or different organic cationic precursor molecules". It is unclear to which of these "the precursor molecules" refers.

Claims 1, 2, 5-7, 19-33, 37-41, 45, and 46 are indefinite because it is unclear what are the metes and bounds a "recipient backbone". It is unclear what the "recipient backbone" is constituted of, and what it is intended to receive. The specification does not define the term, and it is not a term of art, so one of skill in the art cannot envision the claimed recipient backbone or know what are the metes and bounds of the claims.

Claims 6 and 7 are indefinite because they recite "the functional group for binding to nucleic acid molecules" without antecedent basis.

Claims 8-18 and 49 are indefinite because they recite "the organic cationic precursor molecule" without proper antecedent basis. There are at least two antecedents: "identical or different organic cationic precursor molecules". It is unclear to which of these "the precursor molecule" refers.

Claim 11 is indefinite because it is unclear whether "an ornithine radical" and "a S-galactosyl radical" are intended to be substituents of the –C(=O)-C1-C4 alkyl group or definitions of "R2".

Claims 19-21 are indefinite because they recite "the cationic precursor molecule" without proper antecedent basis.

Claim 20 is indefinite because it is unclear what are the metes and bounds of a spermine derivative. It is unclear to what extent spermine may be modified and still be considered by Applicant to be a derivative. Many cationic molecules contain primary amine groups which could be obtained from spermine through organic synthetic reactions. Are all of these considered to be spermine derivatives?

Claims 24-26 are indefinite to the extent that they depend from claim 1, because they recite "the nucleic acid molecule" without proper antecedent basis. The antecedent for nucleic acid molecule is "one or more", so to the extent that the claims read on more than one nucleic acid molecule, it is unclear to which nucleic acid molecule they refer.

Claim 40 is indefinite because it recites "the nucleic acid template" without antecedent basis.

Claim 41 is indefinite because it recites the term "mild", which is a relative term. The term " mild " is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Specifically, the parameter of "oxidative conditions" is rendered indefinite by the use of the term "mild".

Claims 45 and 46 are indefinite because they recite the term "suitable", which is a relative term. The term " suitable " is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Specifically, the parameter of "buffers" is rendered indefinite by the use of the term "suitable".

Claim 46 is indefinite because it recites "the cationic molecules" without proper antecedent basis.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 5-7, 19-33, 37-41, 45, and 46 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 2, 5-7, 19-33, 37-41, 45, and 46 are drawn to the genus of transfection particles comprising organic cationic precursor molecules. The

specification does not provide an adequate written description of the genus of organic cationic precursor molecules embraced by the claims.

The organic precursor molecules are required to have particular structural and functional characteristics. The precursor molecules must function to condense nucleic acid molecules, form covalent crosslinks with each other without crosslinking the nucleic acid molecules, and must form a transfection particle. Structurally, the precursor molecules must comprise at least one lipophilic residue, a non-toxic backbone, a cationic group, and a functional group that allows covalent bond formation with other cationic precursor molecules. The claims do not limit the relationships between the structural characteristics. As a result the number of structures potentially embraced by the claims is vast. For example, the functional group for crosslinking, the cationic group, the backbone, and the lipophilic group may be attached to each other in any combination without structural limitation, e.g. the crosslinking group could be attached to the cationic group, which could be attached to the lipophilic group, which could be attached to the backbone. Also, claims embrace embodiments in which, for example, the lipophilic group and backbone are one and the same. Furthermore, because the claim requires only that the precursor molecules must "comprise" the structural features described above, the precursor molecules may also have other undisclosed structural moieties to which the required elements are bound in unlimited combinations. As a result the genus of possible structures is extremely large.

The specification discloses by structure a large number of species of the genus of organic cationic precursor molecules at pages 7-16 and instant claims 8-18 and 49. Each of these species has an amphiphilic structure and can be considered to be a detergent. The specification discloses at page 4, third paragraph that in a preferred embodiment the precursor molecules are detergent molecules. The specification does not disclose any molecules that comprise the structural elements recited by claim 1, but that do not have an amphiphilic structure, and which are not detergent molecules. However, amphiphilic detergent molecules are only a fraction of the molecules embraced by the claimed genus of cationic precursor molecules. As a result one of skill in the art would conclude that the specification discloses a representative number of species of cationic precursor molecules that are amphiphilic detergents, but could not conclude that the specification adequately describes the rest of the genus. Accordingly the scope of cationic precursor molecules should be limited to those that are also amphiphilic detergent molecules.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 6, 7, 19, 20, 22, 27, 30-32, and 48 are rejected under 35 U.S.C. 102(b) as being anticipated by Wu et al (US Patent 5,166,320, issued 1/24/92).

Wu teaches transfection particles comprising DNA or RNA molecules and polylysine or polyarginine. See abstract; Fig. 1; and column 4, lines 39-44. Each of these polymers comprises precursor molecules (lysine or arginine residues) that are linked to each other by covalent bonds without forming covalent cross links with the nucleic acid molecules. Each of the precursors comprised an amine functional group for formation of polymers, a cationic group for nucleic acid interaction, a non-toxic backbone, and lipophilic residues, including the alpha carbon and side chain carbons. Polyarginine contains a guanidine group which can be considered to be a polyamine. With regard to instant claim 20, drawn to cationic precursor molecules that are spermine derivatives, polylysine and polyarginine are considered to comprise a spermine derivative inasmuch as they contain amines which could have been derived from spermine. Pertinent to claim 22, polyarginine and polylysine are degradable by proteases. Targeting residues include polypeptides and galactose residues. See paragraph bridging columns 5 and 6.

It is noted that claim 1 and dependents are product by process claims wherein the process requires the formation of a complex between precursor

molecules prior to polymerization or dimerization, and that Wu does not teach this step. However, the product of Wu is indistinguishable from the claimed product, regardless of the steps taken to make the products. The Office does not have the facilities for examining and comparing Applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally or structurally different than those taught by the prior art and to establish patentable differences. See Ex parte Phillips, 28 USPQ 1302, 1303 (BPAI 1993), In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ2d 1922, 1923 (BPAI 1989).

Thus Wu anticipates the claims.

Claims 1, 2, 5, 6, 19, 20, 22-32, 40, 41, and 48 are rejected under 35 U.S.C. 102(e) as being anticipated by Wolff et al (US Patent 6,126,964, issued 10/3/00), as evidenced by Fessenden (In Organic Chemistry, Willard Grant Press, 1979).

Wolff teaches methods of making transfection particles wherein DNA or RNA serves as a template for polymerization of amphipathic molecules comprising cationic amine head groups and hydrophobic tails, and wherein the nucleic acid is condensed. See abstract; sentence bridging columns 7 and 8; compounds 10 and 11 at column 10; and column 11, lines 16-18. The

monomers comprise functional groups for polymerization including thiols, hydrazides, aldehydes, amines, and compounds capable of forming enamine linkages. See column 7, lines 3-7 and 25-31. The quaternary amine precursors of Wolff are considered to be detergents in light of Fessenden who taught that quaternary ammonium lipids are used as detergents. See page 722, first full paragraph. Wolff exemplifies lipophilic residues including amides and esters. See e.g. compounds 10-13 at columns 23 and 24. The cationic monomers may be polyamines. See e.g. compounds 6, 7, and 12 at columns 21, 22, and 24. With regard to instant claim 20, drawn to cationic precursors molecules that are spermine derivatives, each of structures 6, 7, and 10-14 is considered to comprise a spermine derivative inasmuch as these compounds contain amines, and $N(CH_2)_3N$ groups, which could have been derived from spermine. Also pertinent to claim 20, Wolff teaches that the compositions may be made by polymerizing spermine itself (column 7, lines 48-57), and spermine could be construed as having both cationic and lipophilic moieties, as well as a non-toxic backbone. Wolff also teaches monomolecular complexes comprising plasmid DNA. See e.g. Fig. 1, column 2, lines 40-51. The monomers may comprise protein ligands, galactose, or fusogenic agents which are covalently attached. See column 8, lines 14-27 and 42-50. The complexes may form part of a supramolecular complex comprising an additional, preformed nucleic acid-binding polymer, that contains a targeting group. See column 10, lines 29-45.

Thus Wolff anticipates the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 27, 27-39, 45, and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wolff et al (US Patent 6,126,964, issued 10/3/00).

Wolff teaches methods of making transfection particles wherein DNA or RNA serves as a template for polymerization of amphipathic molecules comprising cationic amine head groups and hydrophobic tails, and wherein the nucleic acid is condensed. See abstract; sentence bridging columns 7 and 8; compounds 10 and 11 at column 10; and column 11, lines 16-18. The monomers comprise functional groups for polymerization including thiols, hydrazides, aldehydes, amines, and compounds capable of forming enamine linkages. See column 7, lines 3-7 and 25-31. The monomers may comprise protein ligands, galactose, or fusogenic agents which are covalently attached. Alternatively, such targeting groups may be added after polymerization. See column 8, lines 10-27 and 42-50. The complexes may form part of a supramolecular complex comprising an additional, preformed nucleic acid-binding polymer, that contains a targeting group. See column 10, lines 29-45. Wolff also discloses other targeting groups that function after binding to the cell surface, including endosomolytic agents. Finally, Wolff teaches a kit comprising

a receptacle comprising reagents necessary for making the particles. See claim 11.

Wolf does not explicitly teach that the compound capable of forming an enamine should be an ethylene residue as required by instant claim 1. However, the functional groups of Wolff capable of forming enamines must by definition include alkyl groups. MPEP 2144.09 states that a prima facie case of obviousness may be made when chemical compounds have very close structural similarities and similar utilities. Compounds which differ by the successive addition of the same chemical group, e.g., by -CH2- groups) are generally of sufficiently close structural similarity that there is a presumed expectation that such compounds possess similar properties. In re Wilder, 563 F.2d 457, 195 USPQ 426 (CCPA 1977). See also In re May, 574 F.2d 1082, 197 USPQ 601 (CCPA 1978) (stereoisomers prima facie obvious). As such the limitation of the functional group to an ethylene group is considered obvious in view of the disclosure of an alkyl group.

Wolff does not explicitly state that fusogenic peptides or adenovirus should be covalently linked to the particles. However, Wolff does state that targeting moieties can be covalently linked to the particles, and lists endosomolytic agents as targeting agents. See column 8, lines 28-33. Furthermore, Wolff discloses that the prior art taught the use of fusogenic peptides and adenovirus as endosomolytic agents. See sentence bridging columns 1 and 2. As such it would have been obvious to one of ordinary skill in

the art at the time of the invention to attach covalently to the particles of Wolff endosomolytic agents such as fusogenic peptides or adenovirus.

Wolff does not explicitly state that the claimed kit should comprise buffers or other reagents or mechanical devices useful for the preparation of the transfection particle. However, Wolff discloses buffers and reagents required to prepare the complexes, and it would have been obvious to include in the claimed kit these items, as well as mechanical devices such as a gel apparatus for characterization of the complexes (see paragraph bridging columns 17 and 18), because one of skill in the art appreciates that organizing experimental reagents and devices prior to use is standard laboratory practice which reduces the frequency of errors.

Claims 1, 27, 31, and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wolff et al (US Patent 6,126,964, issued 10/3/00) in view of Szoka et al (US Patent 5,661,025, issued 8/26/97).

Wolff teaches methods of making transfection particles wherein DNA or RNA serves as a template for polymerization of amphipathic molecules comprising cationic amine head groups and hydrophobic tails, and wherein the nucleic acid is condensed. See abstract; sentence bridging columns 7 and 8; compounds 10 and 11 at column 10; and column 11, lines 16-18. The monomers comprise functional groups for polymerization including thiols, hydrazides, aldehydes, amines, and compounds capable of forming enamine linkages. See column 7, lines 3-7 and 25-31. The monomers may comprise

protein ligands, galactose, or fusogenic agents which are covalently attached. Alternatively, such targeting groups may be added after polymerization. See column 8, lines 10-27 and 42-50.

Wolff does not teach the use of mannose as a targeting agent.

Szoka teaches methods of targeting dendrimer/nucleic acid complexes to cells by use of a variety of targeting ligands including proteins and sugar residues. Targeting ligands are selected on the basis of the cell one wishes to target. See paragraph bridging columns 13 and 14. Szoka teaches that mannose may be used as targeting ligand.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use mannose as a targeting ligand in the invention of Wolff. The selection of a targeting ligand is simply a matter of design choice that is influenced by the cell on wishes to target. Because Szoka suggests that mannose can be used as a targeting ligand in a nucleic acid delivery composition, it would have been obvious to use it in the composition of Wolff in which the selection of targeting ligands is not limited.

Conclusion

No claim is allowed. Claims 8-18 and 21 are free of the prior art of record.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday

through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, John Leguyader, be reached at 571-272-0760. The official central fax number is 703-872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Richard Schnizer, Ph.D.